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Adjuvant treatment and analysis of failures in patients with high-risk FIGO Stage Ib–II endometrial cancer: An Italian multicenter retrospective study (CTF study)

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HIGHLIGHTS

- Adjuvant chemotherapy reduces the risk of distant recurrences in patients with high-risk, early- stage endometrial cancer with negative pelvic nodes.
- The sequential administration of adjuvant chemotherapy and radiotherapy achieves excellent local and distant control of disease in this clinical settings.

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ABSTRACT

Objectives. The purpose of this retrospective study was to assess the clinical outcome of patients with high-risk, early-stage endometrioid endometrial cancer (stage Ib or II with myometrial invasion >50%, grade 2–3).

Methods. We assessed 192 patients who underwent hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy, had histologically negative pelvic nodes, and had negative CT findings for aortic node involvement.

Results. Tumor relapsed in 36 patients after a median time of 21.2 months. The recurrence was vaginal in 7 (19.4%), distant in 16 (44.4%), aortic in 8 (22.2%), and involved multiple sites in 5 (13.9%). There was a trend to a lower vaginal recurrence rate in the 143 patients who received adjuvant radiotherapy (+chemotherapy) compared with the 46 who did not (2.1% versus 8.7%). Distant or aortic recurrences were lower in the 37 patients who received adjuvant chemotherapy (+radiotherapy) than in the 152 who did not (2.7% versus 18.4%, $p = 0.02$). Of the 29 patients who received sequential adjuvant chemotherapy and radiotherapy, none developed local recurrence and only one had distant recurrence. There was a trend for a better 5-year progression-free survival and overall survival for the patients who received chemotherapy (+radiotherapy) compared with those who did not (86.0% versus 71.3%, and 92.3% versus 75.6%, respectively).

Conclusions. Our data appear to suggest that adjuvant chemotherapy reduces the risk of distant or aortic recurrences and that sequential adjuvant chemotherapy and radiotherapy achieve an excellent local and distant control of disease in these clinical settings.

Introduction

Primary treatment of endometrial cancer is surgery, i.e. extrafascial hysterectomy and bilateral salpingo-oophorectomy with or without pelvic and para-aortic lymph node dissection via either laparotomy or minimally invasive approach [1–4]. On the other hand, although the performance of lymphadenectomy is required by the International Federation of Gynecologic and Obstetrics [FIGO] staging system [5,6], there is yet no consensus about whether and which kind of lymphadenectomy should be carried out in the surgical staging of this malignancy [7–12]. Outside clinical trials, this surgical procedure is usually performed in women with poorly differentiated grade (G_3) (assessed on preoperative biopsy) and/or or deep myometrial invasion (assessed on preoperative magnetic resonance imaging or intra-operative sections). Of the 7990 surgically staged endometrial cancer patients

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reported in the FIGO Annual Report n. 26, 1054 patients had stage Ia disease, 2833 had stage Ib (1988) disease, 1426 had stage Ic disease, 430 had stage IIa disease and 543 had stage IIb disease, and their 5-year overall survival rates were 90.8%, 91.1%, 85.4%, 83.3%, and 74.2%, respectively [5]. Survival of women with surgical stage I and II endometrial cancer was strictly dependent on tumor grade. In fact, 5-year overall survival rates were 92.9% for patients with well differentiated grade [G_1] stage I disease, 89.2% for those with moderately differentiated grade [G_2] stage I disease and 78.9% for those with poorly differentiated [G_3] stage I disease (hazard ratio [HR] = 2.8, 95% confidence interval [CI] = 2.2–3.6), respectively. In the same series, 5-year overall survival rates were 86.0% for patients with G_1 stage II disease, 80.0% for those with G_2 stage II disease, and 66.0% for those with G_3 stage II disease (HR = 2.3, 95% CI = 1.4–3.5). The FIGO staging system has been updated in 2009 [6].

The role of adjuvant treatment in early stage endometrial cancer is still to be defined [13]. External beam pelvic irradiation [EBRT] significantly reduces the risk loco-regional recurrence, without any significant impact on cancer-related deaths or overall survival [14–21]. Although recurrent disease occurs in less than 20% of patients with clinically early endometrial cancer, most of these failures involve distant sites. Postoperative platinum-based chemotherapy reduces the risk of developing the first recurrence outside the pelvis [22–24], and the pooled analysis of two randomized clinical trials (NSGO-EC-9501/EORTC-55991 and MANGO ILIADE-III) has shown that the addition of adjuvant chemotherapy to radiotherapy improves progression-free survival in operated endometrial cancer patients with no residual tumor and a high-risk profile [25]. However most studies comparing adjuvant chemotherapy versus adjuvant radiotherapy or sequential adjuvant chemotherapy and radiotherapy versus adjuvant radiotherapy included heterogenous groups of women, i.e. both patients with stage I–II disease with deep myometrial invasion and G_3 grade and those with advanced stages of disease.

The aim of this retrospective study was to assess the adjuvant treatment and the pattern of failures of patients with high-risk, surgical stage Ib–II endometrioid-type endometrial cancer.

Materials and methods

This retrospective investigation assessed 192 patients who underwent peritoneal washing, standard extrafascial (Piver–Rutledge class I) or modified radical (Piver–Rutledge class II) hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy for FIGO stage Ib, G_{2-3} endometrioid-type endometrial cancer or FIGO stage II, G_{2-3} endometrioid-type endometrial cancer with myometrial invasion >50% at the Department of Gynecology and Obstetrics of the University of Pisa, Turin and Brescia between 1991 and 2012. These patients represented all women with these high-risk factors treated at our centers during the time period. Eighteen patients underwent also aortic lymphadenectomy. All the patients had histologically negative pelvic, and, when removed, aortic nodes negative. The 174 patients who did not undergo aortic lymphadenectomy had negative computed tomography (CT) findings for node aortic involvement. Abdomen-pelvis CT scan was performed two to three weeks before surgery, and aortic nodes were defined negative when their short axes were <5 mm.

One hundred and forty-eight women were operated via laparotomy and forty-four via minimally invasive approach (laparoscopy or robotics). The patients who underwent laparotomic or laparoscopic hysterectomy without pelvic lymphadenectomy, those who underwent vaginal hysterectomy, and those who had synchronous endometrial and ovarian cancer were excluded from the present analysis.

The histological classification was performed according to World Health Organization classification. The architectural grade was defined as follows: G_1, <5% of non-squamous or non-morular solid growth pattern; G_2, 6–50% of non-squamous or non-morular solid growth pattern; and G_3, >50% of non-squamous or non-morular solid growth pattern. Notable nuclear atypia, inappropriate for the architectural grade, raised the grade of G_1 or G_2 tumor by one.

Post-operative treatment was given without well-defined protocols and was established on the basis of pathological findings on surgical specimens, patient age and general conditions.

Some patients had been enrolled in randomized clinical trials comparing radiotherapy versus chemotherapy [22] or radiotherapy versus sequential chemotherapy and radiotherapy [25]. Anyway, adjuvant therapy has been changed in the different centers over long interval time of the study. In particular chemotherapy has been increasingly used after 2008.

EBRT was performed with a 15–18 MV beam, and a 45–50.4 Gy dose was given in daily fractions of 1.8 Gy in 5–6 weeks. The pelvic target volume was outlined on a CT scan. When performed, 45 Gy para-aortic irradiation was planned in daily fractions of 1.8 Gy in 5 weeks. Vaginal cuff high-dose rate brachytherapy (VBT) was added in selected cases with isthmus or stromal cervical involvement after EBRT with a cylinder applicator. The prescribed dose was 10–15 Gy in 5 Gy fractions. Rectal and bladder doses were estimated from dose volume histograms on CT-based plans and were evaluated to the dose points specified by the International Commission on Radiation Units and Measurements [26]. Adjuvant chemotherapy consisted of platinum-based regimens. Radiotherapy was delivered sequentially after chemotherapy in patients who received both adjuvant treatments.

Follow-up procedures are reported in a previous paper [27]. All the patients but 3 have been periodically followed until September 2013 or until death.

The 3 patients lost to follow-up were excluded from recurrence and survival analyses. The median follow-up of survivors was 57 months (range, 9 to 225 months).

Statistical analysis

Patient age, FIGO substage, tumor grade, isthmus involvement, type of radical hysterectomy and adjuvant treatment were analyzed for association with recurrence risk, progression-free survival and overall survival.

Peritoneal, hematogenous, and lymph node recurrences outside the retroperitoneal area (i.e. inguinal,or axillary and supraclavicular) were considered as distant failures. SAS statistical package (release 8.2; SAS Institute, Cary, NC, USA) was used for the computations.

The rates of recurrences were compared to the explicative variables using Pearson's χ^2 test (or two-tailed Fisher's exact test when appropriate).

The time from surgery to the detection of recurrence was defined as progression-free survival. The time from surgery to death or last observation was defined as overall survival. The cumulative probability of progression-free survival and overall survival was estimated by the product-limit method. The log-rank test was used to compare the homogeneity of progression-free survival and overall survival functions across strata defined by categories of prognostic variables.

Results

Patient characteristics and adjuvant treatments are shown in Table 1.

Ninety-four patients had G_2 stage Ib disease, 65 had G_3 stage Ib disease, 14 had G_2 stage II disease, and 16 had G_3 stage II disease.

Surgical approach was open in 148, laparoscopic in 26, and robotic in 18. Of the 192 patients, 38 had no further treatment, 127 had radiotherapy only, and 37 had chemotherapy with or without radiotherapy.

Chemotherapy consisted in: i) carboplatin + paclitaxel (n. 3 patients) or cisplatin + cyclophosphamide (n. 4) or cisplatin + epirubicin + paclitaxel (n. 1) for 6 cycles in the patients who had chemotherapy only; ii) carboplatin + paclitaxel (n.12), cisplatin + epirubicin/doxorubicin (n. 5) or cisplatin + epirubicin + paclitaxel

Table 1
Patient characteristics and postoperative adjuvant treatment.

Age (years)	64, median (range, 32–86)
FIGO stage	
Ib	161
II	31
FIGO grade	
G_2	110
G_3	82
Isthmus involvement	
Yes	33
Not	159
Adjuvant treatment	
No further treatment	38
EBRT[a]	105[a]
VBT	12
Chemotherapy	8
Chemotherapy + EBRT[b]	18[b]
Chemotherapy + VBT	11

Legend: G2, moderately differentiated; G3; poorly differentiated; EBRT, external beam radiotherapy; VBT, vaginal brachytherapy.
[a] VBT was added in 11 pts.
[b] VBT was added in 4 pts.

(n. 1) for 4 cycles in the patients who had chemotherapy followed by EBRT; and iii) carboplatin + paclitaxel (n. 9) or single-agent carboplatin (n. 2) for 4–5 cycles in the patients who had chemotherapy followed by VBT.

Table 2 reported patient and tumor characteristics according to postoperative treatment (no adjuvant treatment, radiotherapy only, chemotherapy with or without radiotherapy). By the χ square test, postoperative treatment was not related to patient age ($\chi^2 = 3.45$, p = ns), isthmus involvement ($\chi^2 = 4.84$, p = ns) and tumor grade ($\chi^2 = 0.728$, p = ns). Radiotherapy was more frequently used in patients with FIGO stage II disease ($\chi^2 = 6.14$, $p = 0.047$). Therefore the differences in treatment selection did not appear to influence the outcome.

Tumour relapsed in 36 (19.0%) of 189 patients. Recurrence developed within 12 months in 13 patients (36.1%), between 12 and 24 months in 9 (25.0%), and after 24 months in 14 (38.9%). The median time to relapse was months 21.2 (range, 3–185 months). The recurrence was vaginal in 7 (19.4%), distant in 16 (44.4%) (lung, 8; peritoneum, 4; lung + peritoneum, 2; liver, 1; bone, 1), aortic in 8 (22.2%), and involved multiple sites in 5 (13.9%) (aortic nodes + liver, 1; pelvic nodes + peritoneum in 1; pelvic nodes + bone in 1; vagina + pelvic nodes + lung in 1; vagina + lung in 1). No patients had an isolated pelvic node recurrence.

There was a trend to a lower isolated vaginal recurrence rate in the 143 patients who received adjuvant radiotherapy (with or without chemotherapy) compared with the 46 who did not (2.1% versus 8.7%, $p = 0.06$) (Table 3).

Distant or aortic recurrences were significantly lower in the 37 patients who received adjuvant chemotherapy (with or without radiotherapy) compared with the 152 patients who did not (2.7% versus 18.4%, $p = 0.02$) (Table 4).

Table 3
Isolated vaginal recurrence rate according to clinical–pathological variables and treatment modalities (7 patients).

Variables	Pts	Recurrence		*P* value
	N	N	(%)	
Age				
<64 years	85	1	1.2	0.13
>64 years	104	6	5.8	
FIGO stage				
Ib	159	5	3.1	0.0006
II	30	2	6.7	
FIGO grade				
G2	108	3	2.8	0.46
G3	81	4	4.9	
Isthmus involvement				
Yes	34	2	5.9	0.61
Not	155	5	3.2	
Type of hysterectomy				
Type I	143	5	3.5	0.64
Type II	46	2	4.3	
Adjuvant treatment				
No further treatment	38	2	5.3	
EBRT	102[a]	3	3.1	
VBT	12	0	0	
Chemotherapy	8	2	25	
Chemotherapy + EBRT	18[b]	0	0	
Chemotherapy + VBT	11	0	0	
Adjuvant radiotherapy				
No radiotherapy[c]	46	4	8.7	0.06
Radiotherapy[d]	143	3	2.1	
Adjuvant chemotherapy				
No chemotherapy[e]	152	5	3.3	0.62
Chemotherapy[f]	37	2	5.4	

Legend: EBRT, external beam radiotherapy; VBT, vaginal brachyterapy.
[a] VBT was added in 10 pts.
[b] VBT was added in 4 pts.
[c] Chemotherapy or no further treatment.
[d] With or without chemotherapy.
[e] Radiotherapy or no further treatment.
[f] With or without radiotherapy.

Of the 29 patients who received sequential adjuvant chemotherapy and radiotherapy, none developed local recurrence and only one (3.4%) had distant recurrence.

Progression-free survival and overall survival were significantly associated with patient age ($p = 0.0025$ and $p = 0.0017$, respectively), FIGO stage ($p = 0.035$ and 0.0103, respectively), and isthmus involvement ($p = 0.0271$ and 0.0280) (Table 5a and b).

There was a trend for a better 5-year progression-free survival and 5-year overall for the patients who received adjuvant chemotherapy (with or without radiotherapy) compared with those who did not (86.0% versus 71.3%, and 92.3% versus 75.6%, respectively) (Fig. 1). Conversely, adjuvant radiotherapy did not impact on progression-free survival and overall survival (Fig. 2).

Table 2
Patient and tumor characteristics according to postoperative treatment.

Variables	Age		FIGO stage		Isthmus involvement		FIGO grade	
	<64	≥64	Ib	II	Yes	not	G2	G3
No therapy 38 pts	12	26	34	4	5	33	24	14
RT 114 pts	55	59	90	24	26	88	63	51
Chemotherapy ± RT 37 pts	18	19	35	2	3	34	21	16
χ^2, *p* value	3.45	ns	6.14	0.047	4.84	ns	0.728	ns

Legend: RT, radiotherapy.

Table 4
Distant or aortic nodal recurrence rate according to clinical–pathological variables and treatment modalities (29 patients [a]).

Variables	Pts	Recurrence		*P* value
	N	*N*	(%)	
Age				
<64 years	85	11	12.9	0.43
>64 years	104	18	17.3	
FIGO stage				
Ib	159	20	12.5	0.025
II	30	9	30.0	
FIGO grade				
G_2	108	15	13.8	0.55
G_3	81	14	17.2	
Isthmus involvement				
Yes	34	10	29.4	0.0018
Not	155	19	12.2	
Type of hysterectomy				
Type I	143	21	14.7	0.64
Type II	46	8	17.4	
Adjuvant treatment				
No further treatment	38	7	18.4	
EBRT	102[b]	17	16.6	
VBT	12	4	33.3	
Chemotherapy	8	0	0	
Chemotherapy + EBRT	18[c]	1	5.5	
Chemotherapy + VBT	11	0	0	
Adjuvant radiotherapy				
No radiotherapy[d]	46	8	17.4	0.64
Radiotherapy[e]	143	21	14.7	
Adjuvant chemotherapy				
No chemotherapy[f]	152	28	18.4	0.02
Chemotherapy[g]	37	1	2.7	

Legend: EBRT, external beam radiotherapy; VBT, vaginal brachyterapy.
[a] Concomitant local and/or pelvic recurrence in 4 pts.
[b] VBT was added in 10 pts.
[c] VBT was added in 4 pts.
[d] *Chemotherapy or no further treatment.*
[e] With or without chemotherapy.
[f] Radiotherapy or no *further treatment.*
[g] With or without radiotherapy.

Discussion

An updated Cochrane systematic review of eight trials comparing the efficacy and toxicity of adjuvant radiotherapy versus no treatment in stage I endometrial cancer showed that EBRT significantly reduced loco-regional recurrence compared with no EBRT (or VBT alone) (HR = 0.36, 95%CI = 0.25–0.52, $p < 0.001$), without any improvement in overall survival (HR = 0.99, 95% CI = 0.82–1.20), endometrial cancer-specific survival (HR = 0.96, 95% CI = 0.72–1.28), or distant recurrence rates (relative risk [RR] = 1.04, 95% CI = 0.80–1.35) [21]. EBRT was associated with an increased risk of severe acute toxicity, severe late toxicity, and reduced quality of life. A prior meta-analysis had led to similar conclusions, and had suggested that EBRT was detrimental for low-risk endometrial cancer (stage Ia, G_{1-2}) (odd ratio [OR] for OS = 0.71; 95%CI = 0.52–0.96), did not affect overall survival in intermediate risk disease (either stage Ia G_3 or stage Ib G_{1-2}) (OR = 0.97; 95%CI = 0.69–1.35), and offered a significant benefit in clinical outcome in high-risk disease (stage Ib G_3) (OR = 1.76; 95%CI = 1.07–2.89) [19]. All the evidences point to the direction that patients with low- and intermediate-risk disease do not benefit from adjuvant EBRT and that, otherwise, high-risk patients could have some advantage. The randomized PORTEC-2 trial compared adjuvant VBT versus EBRT in 427 patients with high-intermediate risk endometrial cancer [28].

Table 5
Variables predictive of progression-free survival and overall survival.

a) Progression-free survival

Variables	Pts	2-year PFS	5-year PFS	*P* value
Age				
<64 years	85	95.1%	83.4%	0.0025
>64 years	104	80.5%	66.0%	
FIGO stage				
Ib	159	89.3%	77.8%	0.035
II	30	76.1%	56.5%	
FIGO grade				
G_2	108	89.4%	79.1%	0.1891
G_3	81	85.5%	67.8%	
Isthmus involvement				
Yes	34	81.7%	60.1%	0.0271
Not	155	88.4%	77.5%	
Type of hysterectomy				
Type I	143	88.1 %	75.0%	0.9888
Type II	46	84.0 %	71.2%	
Adjuvant treatment				
Yes	151	88.9%	75.3%	0.2373
Not	38	80.1%	69.3%	
Adjuvant radiotherapy				
Not radiotherapy[a]	46	83.8%	69.7%	0.2421
Radiotherapy[b]	143	88.3%	75.7%	
Adjuvant chemotherapy				
Not chemotherapy[c]	152	84.7%	71.3%	0.1612
Chemotherapy[d]	37	100.0%	86.0%	

b) Overall survival

Variables	Pts	2-year OS	5-year OS	*P* value
Age				
<64 years	85	100%	86.4%	0.0017
>64 years	104	89.5%	71.4%	
FIGO stage				
Ib	159	95.3%	83.1%	0.0103
II	30	85.9%	58.1%	
FIGO grade				
G_2	108	93.9%	83.2%	0.2599
G_3	81	93.5%	72.5%	
Isthmus involvement				
Yes	34	93.8%	61.2%	0.0280
Not	155	93.7%	82.9%	
Type of hysterectomy				
Type I	143	94.0%	78.2%	0.7339
Type II	46	92.6%	79.2%	
Adjuvant treatment				
Yes	151	94.3%	80.4%	0.2030
Not	38	91.0%	71.6%	
Adjuvant radiotherapy				
Not radiotherapy[a]	46	92.8%	76.8%	0.4512
Radiotherapy[b]	143	94.0%	79.1%	
Adjuvant chemotherapy				
Not chemotherapy[c]	152	92.1%	75.6%	0.1619
Chemotherapy[d]	37	100.0%	92.3%	

Legend: Pts, patients; PFS, progression-free survival, OS, overall survival.
[a] Chemotherapy or no further treatment.
[b] With or without chemotherapy.
[c] Radiotherapy or no further treatment.
[d] With or without radiotherapy.

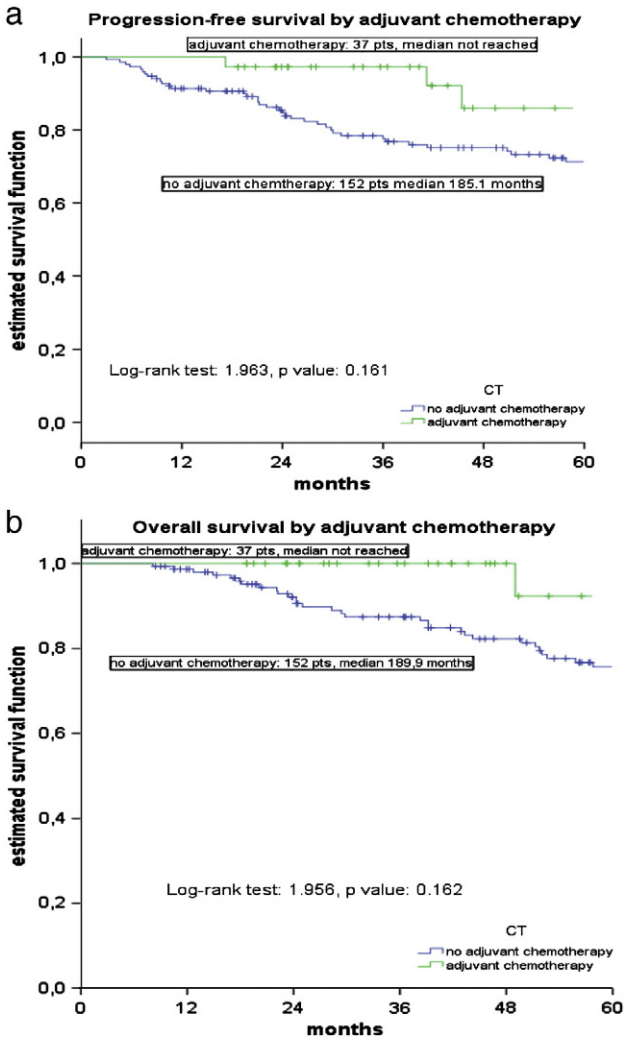

Fig. 1. Progression-free survival (a) and overall survival (b) by adjuvant chemotherapy.

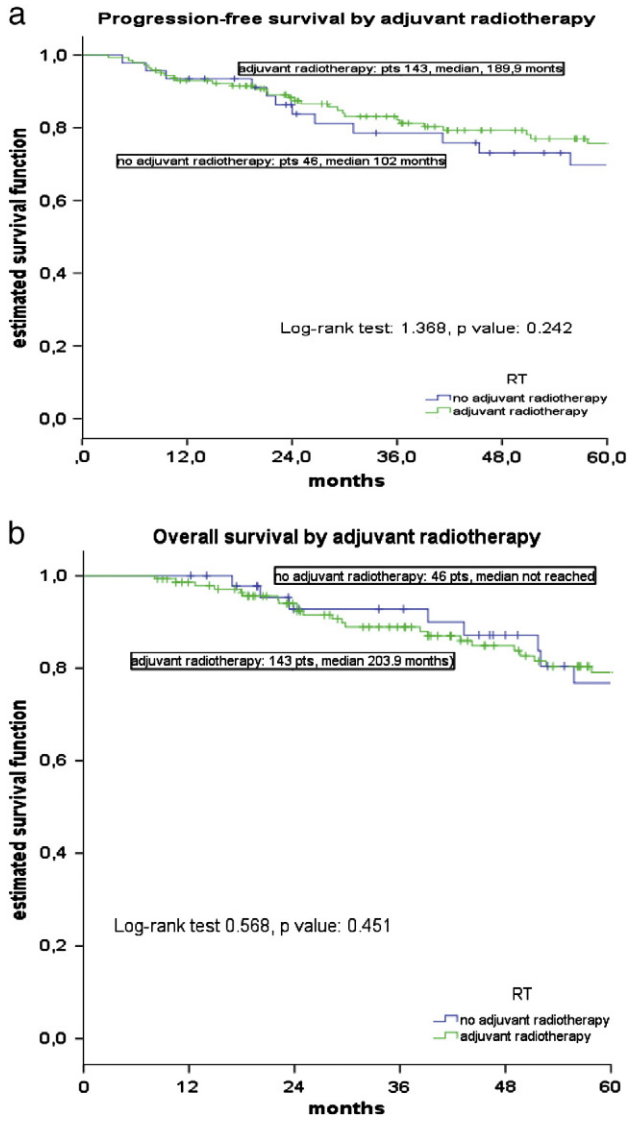

Fig. 2. Progression-free survival (a) and overall survival (b) by adjuvant radiotherapy.

These two adjuvant treatments obtained similar results in terms of vaginal recurrence rates, loco-regional relapse rates, distant metastasis rates, disease-free survival and overall survival, but the incidence of acute grade 1–2 gastrointestinal toxicity was significantly lower in the VBT arm than in the EBRT arm (12.6% versus 53.8%). Therefore VBT could be the adjuvant treatment of choice in this clinical setting.

Four randomized trials compared adjuvant platinum based chemotherapy to radiotherapy in high-risk endometrial cancer [22,23,29,30]. The pooled data meta-analyses showed a significant improvement in terms of progression-free survival (HR = 0.80; 95%CI = 0.66–0.97) and overall survival (HR = 0.76, 95% CI = 0.62–0.92) for chemotherapy arm [24]. The HR for death was the same if the analysis excluded the trial enrolling carcinosarcomas [30]. However, GOG122 included patients with stage III–IV endometrial cancer with residual disease <2 cm [29]. The advantage in overall survival for chemotherapy arm was lost if this trial was omitted from the analysis [24]. The GIGOC trial, which enrolled 345 patients with high-risk endometrioid carcinoma (FIGO stage [1988] Ic G_3, IIa–b G_3 with myometrial invasion >50%, stage III disease), showed that EBRT delayed local relapses and chemotherapy delayed metastases but these trends did not achieve statistical significance [22]. No separate analysis was performed in the subset of the 90 women with stage Ic (FIGO 1988) disease and in the subset of the 31 women with stage II disease. The Japanese GOG study, which included 385 women with intermediate- and high-risk endometrioid carcinoma with more than 50% myometrial invasion, failed to detect any difference in progression-free survival and overall survival between chemotherapy and EBRT in the group of patients with FIGO stage Ic (1988) G_{1-2} disease under 70 years old [23]. Conversely, chemotherapy achieved a significantly better progression-free survival (83.8% versus. 66.2%, HR = 0.44; 95% CI = 0.20–0.97) and overall survival (89.7% versus. 73.6%, HR = 0.24, 95% CI = 0.09–0.69) in patients with stage Ic G_3 disease over 70 years old or with stage II or IIIA disease (positive cytology).

The meta-analysis of five randomized trials comparing no additional treatment with additional chemotherapy after hysterectomy and radiotherapy for high-risk endometrial cancer showed that chemotherapy reduced the risk of developing the first recurrence outside the pelvis (RR = 0.79; 95% CI = 0.68–0.92), and achieved a small benefit in progression-free survival (HR = 0.75, 95% CI = 0.64–0.89) and overall survival (HR = 0.74, 95% CI = 0.64–0.89) [24,25,31,32]. The analysis of pelvic recurrence rates was underpowered but the trend suggested that chemotherapy might have an added value when used with radiotherapy (RR = 0.48, 95% CI = 0.20–1.18) [24].

In the present series, tumor relapsed in 36 out of 189 (19.0%) women, with high-risk stage Ib–II endometrioid-type endometrial cancer, and recurrent disease was most often distant. Therefore, the control of systemic dissemination appears to be crucial for the clinical outcome of these patients. Distant or aortic failure rate was significantly lower in patients who received adjuvant platinum-based chemotherapy (with or

without radiotherapy) compared with those who did not (2.7% versus 18.4%, $p = 0.02$). There was a trend for a better 5-year progression-free survival and 5-year overall for the patients who received adjuvant chemotherapy (with or without radiotherapy) compared with those who did not (86.0% versus 71.3% and 92.3% versus 75.6%, respectively). It is noteworthy of the 29 patients who underwent sequential adjuvant platinum-based chemotherapy and radiotherapy none developed local recurrence and only one (3.4%) had distant recurrence.

These results are in agreement with those of a phase II Radiation Therapy Oncology Group [RTOG] trial designed to assess the feasibility and efficacy of adjuvant EBRT concurrent with cisplatin followed by VBT and 4 cycles of platinum-paclitaxel based chemotherapy in patients with high-risk endometrial cancer (grade 2–3 with either >50% myometrial invasion, cervical stromal invasion, or pelvic-confined extra-uterine disease) [33]. In this study, that showed an acceptable toxicity, there were no failures in the 17 patients with stage Ic–IIb (1988) disease, while loco–regional and distant recurrences occurred in 7.4% and 29.6%, respectively, of the 27 patients with stage III disease. The combined therapy approach obtained excellent pelvic and distant control rates in patients with uterine-confined endometrial cancer, whereas patients with stage III disease still experienced a predominant pattern of distant metastases. The importance of this combined adjuvant treatment has been recently confirmed by a retrospective Canadian study including 55 patients with early-stage, high-risk endometrial cancer (two or more risk uterine factors: grade 3, >50% myometrial invasion, or cervical stromal involvement), who received 3 or 4 cycles of carboplatin plus paclitaxel followed by pelvic radiotherapy [34]. After a median follow-up of 27 months, only 4 patients (7.3%) recurred, including three with distant recurrence and one with a pelvic and para-aortic nodal recurrence. A historical cohort in which none of the patients received adjuvant chemo-radiotherapy had a 29.4% recurrence rate, and therefore the HR for recurrence was 0.27 (95% CI = 0.02–4.11).

The strengths of this study are represented by the enrollment criteria that included only a very well defined group of high-risk but early-stage endometrioid-type endometrial cancer patients (which have been grouped with lower risk patients in prior studies), by the length of follow-up, and by the description of rate and pattern of recurrence. The weaknesses of the investigation are represented by the over 20 year period of the study during which adjuvant therapy changed substantially, by the retrospective nature, by the very limited number of aortic lymphadenectomies performed (although all patients had histologically negative pelvic nodes and negative CT findings for node aortic involvement), and by the lack of standardization in postoperative treatment. In any case, our data appear to suggest that adjuvant platinum-based chemotherapy reduces the risk of distant recurrences in patients with high-risk, early-stage endometrioid-type endometrial cancer, and that the sequential administration of adjuvant chemotherapy and radiotherapy achieves an excellent local and distant control of disease in these clinical settings.

Multicenter phase III-randomized trials (PORTEC-3, ENGOT-EN2-DGCG/EORTC 55102) are currently investigating the efficacy of platinum-based chemotherapy, with or without radiotherapy in patients with high-risk endometrial cancer [35,36]. The PORTEC-3 study compares adjuvant radiotherapy versus adjuvant concomitant and sequential radiotherapy and chemotherapy in patients with high-risk endometrial cancer (stage Ib G_3 disease with lymph vascular space involvement, stage Ic–IIa G_3 disease, stage IIb, IIIa or IIIc disease, or stage Ib–III disease with serous or clear cell histology) [35]. ENGOT-EN2-DGCG/EORTC 55102 compares postoperative chemotherapy versus no further treatment in patients with stage I–II medium or high risk endometrial cancer [36].

Chemotherapy or sequential chemotherapy and radiotherapy will probably have a larger and larger use in the adjuvant treatment of high-risk, early-stage endometrioid-type endometrial cancer.

Conflict of interest statement

The authors declare no conflict of interest.

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